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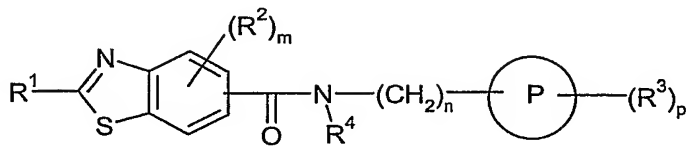
(54) Title: NEW BENZOTHIAZOLECARBOXAMIDES



(I)

(57) Abstract: The present invention relates to new compounds of formula I, (I) wherein R^1 to R^4, m, n and p, are as defined as in formula I, or salts, solvates or solvated salts thereof, processes for their preparation and to a new intermediate used in the preparation thereof, pharmaceutical formulations containing said compounds and to the use of said compounds in therapy.

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NEW BENZOTHIAZOLECARBOXAMIDES

FIELD OF THE INVENTION

The present invention relates to new compounds, to pharmaceutical compositions containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of said compounds and to new intermediate used in the preparation thereof.

BACKGROUND OF THE INVENTION

Pain sensation in mammals is due to the activation of the peripheral terminals of a specialized population of sensory neurons known as nociceptors. Capsaicin, the active ingredient in hot peppers, produces sustained activation of nociceptors and also produces a dose-dependent pain sensation in humans. Cloning of the vanilloid receptor 1 (VR1 or TRPV1) demonstrated that VR1 is the molecular target for capsaicin and its analogues. (Caterina,M.J., et al., et.al. Nature (1997) v.389 p 816-824). Functional studies using VR1 indicate that it is also activated by noxious heat , tissue acidification) and other inflammatory mediators (Tominaga,M., et.al. Neuron (1998) v.21, p.531-543). Expression of VR1 is also regulated after peripheral nerve damage of the type that leads to neuropathic pain. These properties of VR1 make it a highly relevant target for pain and for diseases involving inflammation. While agonists of the VR1 receptor can act as analgesics through nociceptor destruction, the use of agonists, such as capsaicin and its analogues, is limited due to their pungency, neurotoxicity and induction of hypothermia. Instead, agents that block the activity of VR1 should prove more useful. Antagonists would maintain the analgesic properties, but avoid pungency and neurotoxicity side effects.

Compounds with VR1 inhibitor activity are believed to be of potential use for the treatment and/or prophylaxis of disorders such as pain, especially that of inflammatory or traumatic origin such as arthritis, ischaemia, fibromyalgia, low back pain and post-operative pain (Walker et al., J Pharmacol Exp Ther. (2003) Jan; 304(1):56-62). In addition to this visceral pains such as chronic pelvic pain, cystitis, irritable bowel syndrome (IBS), pancreatitis and the like, as well as neuropathic pain such as sciatia, diabetic neuropathy,

HIV neuropathy, multiple sclerosis, and the like (Walker et al *ibid*, J Pharmacol Exp Ther. (2003) Mar;304(3):940-8), are potential pain states that could be treated with VR1 inhibiton. These compounds are also believed to be potentially useful for inflammatory disorders like asthma, cough, inflammatory bowel disease (IBD) (Hwang, et al., Curr Opin Pharmacol (2002) Jun;2(3):235-42). Compounds with VR1 blocker activity are also useful for itch and skin diseases like psoriasis and for gastro-esophageal reflux disease (GERD), emesis, urinary incontinence and hyperactive bladder (Yiangou et al BJU Int (2001) Jun;87(9):774-9, Szallasi, Am J Clin Pathol (2002) 118: 110-21). VR1 inhibitors are also of potential use for the treatment and/or prophylaxis of the effects of exposure to VR1 activators like capsaicin or tear gas, acids or heat (Szallasi *ibid*).

The role for VR1 antagonists in Inflammatory Bowel Diseases (IBD) is further supported by the finding that primary sensory neuron denervation by subcutaneous administration of capsaicin to neonatal rats, resulted in decreased levels of disease activity index (DAI), MPO and histological damage to the gut in DSS colitis model compared to control (N Kihara, et al., Gut, 2003. 52: p. 713-719). TRPV1 antagonists attenuate macroscopic symptoms in DSS colitis model in mice (E. S. KIMBALL, et al., Neurogastroenterol Motil, 2004. 16: p. 1-8).

The potential for a role for VR1 antagonists in Irritable Bowel Syndrome (IBS) has been described. Patients with faecal urgency and rectal hypersensitivity have increased levels of TRPV1 expression in nerve fibres in muscle, submucosal and mucosal layers. This also correlates with increase sensitivity to heat and distension (C L H Chan, et al., THE LANCET, 2003. 361(Feb 1): p. 385-91). Jejunal wide dynamic range (WDR) afferents show lower firing in response to pressure ex vivo in TRPV1-/- mice (Rong W, H.K., et al., J Physiol (Lond). 2004. 560: p. 867-881). The visceromotor responses to jejunal and colorectal distension in rat are affected by a TRPV1 antagonist using both ramp and phasic distensions (Winchester, EMG response to jejunal and colorectal distension in rat are affected by a TRPV1 antagonist in both ramp and phasic distensions. DDW abstract, 2004). Capsaicin applied to the ileum induce pain and mechanical hyperalgesia in human experimental model (Asbjørn Mohr Drewes, et al., Pain, 2003. 104: p. 333-341).

A role in Gastroesophageal Reflux Disease (GERD) for VR1 antagonists has been mentioned in the literature. Patients with oesophagitis have increased levels of TRPV1 expression in peripheral nerves enervating the oesophageal epithelium (P. J. Matthews, et al., European J. of Gastroenterology & Hepatology, 2004. 16: p. 897-902). Even if the TRPV1 antagonist JYL1421 only has minor effects of acid-induced excitation of esophageal afferents, an antagonist with a different profile has yet to be evaluated. Since TRPV1 appears to play a role in mechanosensation, it is possible that antagonists may inhibit TLESRs, the main cause of gastroesophageal reflux.

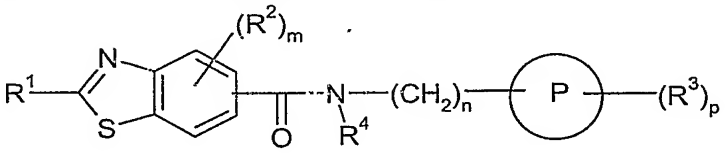
A further portential use relates to the treatment of tolerance to VR1 activators.

VR1 inhibitors may also be useful in the treatment of interstitial cystitis and pain related to interstitial cystitis.

DETAILED DESCRIPTION OF THE INVENTION

The object of the present invention is to provide compounds exhibiting an inhibitory activity at the vanilloid receptor 1 (VR1).

The present invention provides a compound of formula I



(I)

wherein:

ring P is C_{6-10}aryl, C_{3-11}cycloalkyl or C_{5-10}heteroaryl;

R^1 is H, C_{1-4}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, $COOC_{0-6}$alkyl, NH_2, NHC_{1-6}alkyl, $N(C_{1-6}alkyl)_2$, NH(aryl) or $N(aryl)_2$;

R^2 is H, C_{1-4}alkyl, halo, hydroxyC_{0-6}alkyl or C_{1-6}alkylOC_{0-6}alkyl;

m is 0, 1, 2 or 3;

n is 0, 1, 2, 3, 4 or 5;

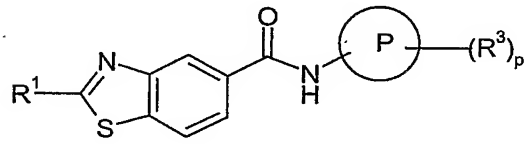
R^3 is NO_2, NH_2C_{0-6}alkyl, halo, $N(C_{1-6}alkyl)_2C_{0-6}$alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{5-6}arylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl, C_{1-6}alkylNC_{0-6}alkyl, $(C_{0-6}alkyl)_2NC(O)C_{0-6}$alkyl, $(C_{0-6}alkyl)_2OC(O)C_{0-6}$alkyl or $(C_{0-6}alkyl)_2C(O)OC_{0-6}$alkyl;

p is 1, 2, 3, 4 or 5; and

R^4 is H, C_{1-6}alkyl, arylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl or $N(C_{1-6}alkyl)_2C_{0-6}$alkyl,

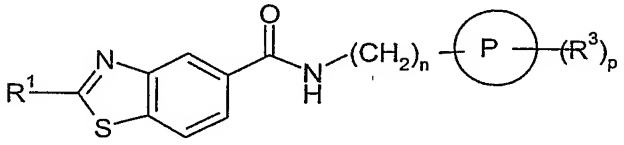
or salts, solvates or solvated salts thereof.

One embodiment of the invention relates to the compound of formula Ib wherein R^1, R^3, m and p, are as defined above, and n is 0 and R^2 and R^4 are H.



(Ib)

One embodiment of the invention relates to the compound of formula Ic, wherein R^1, R^3, m and p, are as defined above, and n is 1, 2, 3, 4 or 5 and R^2 and R^4 are H.



(Ic)

In a further embodiment of the invention P is phenyl.

In yet another embodiment of the invention R^1 is methyl or hydroxyC_{1-3}alkyl. In one embodiment R^1 is methyl, hydroxymethyl, hydroxyethyl or hydroxypropyl.

In another embodiment n is 0, 1 or 2.

In yet a further embodiment R^3 is halo, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{5-6}aryl, C_{1-2}alkylO or $(C_{0-6}alkyl)_2NC(O)C_{0-6}$alkyl.

In another embodiment R^3 is tert-butyl, phenyl, fluoromethyl, difluoromethyl or trifluoromethyl.

One embodiment of the invention relates to compounds selected from the group consisting of

N-4-*tert*-butylphenyl-2-methyl-1,3-benzothiazole-5-carboxamide,

N-4-cyclohexylphenyl-2-methyl-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[2-methyl-4-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[4-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[3-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[2-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[4-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[3-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide,

N-4-methoxy-2-naphthyl-2-methyl-1,3-benzothiazole-5-carboxamide,

N-4-*tert*-butylphenyl-2-hydroxymethyl-1,3-benzothiazole-5-carboxamide,

N-(4-bromophenyl)-2-methyl-1,3-benzothiazole-5-carboxamide,

2-methyl-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-carboxamide,

N-[2-(3-fluorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,

N-(5-isopropoxy-1-naphthyl)-2-methyl-1,3-benzothiazole-5-carboxamide,

2-methyl-N-{2-[4-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazole-5-carboxamide,

N-[2-(4-ethylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,

N-[2-(4-fluorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,

N-[2-(4-tert-butylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,

N-[2-(4-methoxyphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,

N-(4-isopropylphenyl)-2-methyl-1,3-benzothiazole-5-carboxamide,

N-[2-(4-chlorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,

N-[2-(3,4-dichlorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,

N-4-tert-butylphenyl-2-hydroxymethyl-1,3-benzothiazole-5-carboxamide,
2-(hydroxymethyl)-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-carboxamide, and
N-[2-(3-fluorophenyl)ethyl]-2-(hydroxymethyl)-1,3-benzothiazole-5-carboxamide
or salts, solvates or solvated salts thereof.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but are not limited to methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl, i-hexyl or t-hexyl. The term C_{1-3} alkyl having 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl or i-propyl.

The term 'C_0' means "a bond" or "does not exist". For example when R^3 is C_0alkyl, R^3 is a bond and "arylC_0alkyl" is equivalent with "aryl", "C_2alkylOC_0alkyl" is equivalent with "C_2alkylO".

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups. The term "C_{2-6}alkenyl" having 2 to 6 carbon atoms and one or two double bonds, may be, but is not limited to vinyl, allyl, propenyl, butenyl, crotyl, pentenyl, or hexenyl, and a butenyl group may for example be buten-2-yl, buten-3-yl or buten-4-yl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups. The term "C_{2-6}alkynyl" having 2 to 6 carbon atoms and one or two trippel bonds, may be, but is not limited to etynyl, propargyl, pentynyl or hexynyl and a butynyl group may for example be butyn-3-yl or butyn-4-yl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C_{3-7}cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocycloalkyl" denotes a 3- to 7-membered, non-aromatic, partially or completely saturated hydrocarbon group, which contains one ring and at least one heteroatom. Examples of said heterocycle include, but are not limited to pyrrolidinyl, pyrrolidonyl, piperidinyl, piperazinyl, morpholinyl, oxazolyl, 2-oxazolidonyl or tetrahydrofuranyl.

In this specification, unless stated otherwise, the term "aryl" refers to an optionally substituted monocyclic or bicyclic hydrocarbon unsaturated aromatic ring system. Examples of "aryl" may be, but are not limited to phenyl and naphthyl.

In this specification, unless stated otherwise, the term "heteroaryl" refers to an optionally substituted monocyclic or bicyclic ring system whereby at least one ring is aromatic independently from N, O or S. Examples of "heteroaryl" may be, but are not limited to pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl or oxazolyl.

In this specification, unless stated otherwise, the terms "heteroarylalkyl" and "phenylalkyl" refer to a substituent that is attached via the alkyl group to an aryl or heteroaryl group.

In this specification, unless stated otherwise, the terms "halo" and "halogen" may be fluoro, iodo, chloro or bromo.

In this specification, unless stated otherwise, the term "haloalkyl" means an alkyl group as defined above, which is substituted with halo as defined above. The term "C_{1-6}haloalkyl" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl or bromopropyl. The term "C_{1-6}haloalkylO" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy or difluoroethoxy.

Unless specified otherwise within this specification, the nomenclature used in this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts, solvates or solvated salts thereof. Salts for use in pharmaceutical formulations will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

A suitable pharmaceutically acceptable salt of the compounds of the invention is, for example, an acid-addition salt, for example a salt with an inorganic or organic acid. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base.

Other pharmaceutically acceptable salts and methods of preparing these salts may be found in, for example, Remington's Pharmaceutical Sciences (18^{th} Edition, Mack Publishing Co.).

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

The invention also relates to any and all tautomeric forms of the compounds of formula I.

Medical use

Surprisingly, it has been found that the compounds according to the present invention are useful in therapy. The compounds of formula I, or salts, solvates or solvated salts thereof, as well as their corresponding active metabolites, exhibit a high degree of potency and selectivity for individual vanilloid receptor 1 (VR1) groups. Accordingly, the compounds of the present invention are expected to be useful in the treatment of conditions associated with excitatory activation of vanilloid receptor 1 (VR1).

The compounds may be used to produce an inhibitory effect of VR1 in mammals, including man.

VR1 are highly expressed the peripheral nervous system and in other tissues. Thus, it is expected that the compounds of the invention are well suited for the treatment of VR1 mediated disorders.

The compounds of formula I are expected to be suitable for the treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain. Examples of such disorder may be selected from the group comprising arthritis, rheumatoid arthritis, spondylitis and gout, fibromyalgia, low back pain and sciatica, post-operative pain, cancer pain, migraine and tension headache, visceral pains like chronic pelvic pain, cystitis, including interstitial cystitis, pancreatitis, renal and biliary colic, menstruation associated pain, pain related to ischeamic and angina, neuropathic pain disorders such as diabetic neuropathy, HIV neuropathy, chemotherapy induced neuropathies, post-herpetic neuralgia, post traumatic neuralgia and complex regional syndrome as well as itch.

Further relevant disorders may be selected from the group comprising gastro-esophageal reflux disease (GERD), functional gastrointestinal disorders (FGD) such as irritable bowel syndrome (IBS), irritable bowel syndrome (IBS), and functional dyspepsia (FD).

Further examples of disorders are overactive bladder ("OAB"), a term for a syndrome that encompasses urge incontinence, urgency and frequency. Compounds of the invention may alleviate urinary incontinence ("UI") the involuntary loss of urine that results from an inability of the bladder to retain urine as a consequence of either urge (urge incontinence), or physical or mental stress (stress incontinence).
Other relevant disorders may be psoriasis, and emesis.

Yet further relevant disorders are related to respiratory diseases and may be selected from the group comprising cough, asthma, chronic obstructive lung disease and emphysema, lung fibrosis and interstitial lung disease.
The VR1 inhibitor(s) for respiratory use, may be administrated by either an oral or inhaled route. The respiratory disease may be an acute and chronic illness and may be related to infection(s) and/or exposure to environmental pollution and/or irritants.
The compounds of formula I may also be used as antitoxin to treat (over-) exposure to VR1 activators like capsaicin, tear gas, acids or heat. Regarding heat, there is a potential use for VR1 antagonists in (sun-) burn induced pain, or inflammatory pain resulting from burn injuries.
The compounds may further be used for treatment of tolerance to VR1 activators.

One embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, in therapy.

Another embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of VR1 mediated disorders.

A further embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of acute and chronic pain.

Yet another embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of acute and chronic neuropathic pain.

Yet a further embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of acute and chronic inflammatory pain.

One embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of arthritis, rheumatoid arthritis, spondylitis and gout, fibromyalgia, low back pain and sciatica, post-operative pain, cancer pain, migraine and tension headache, visceral pains like chronic pelvic pain, cystitis, including interstitial cystitis, pancreatitis, renal and biliary colic, menstruation associated pain, pain related to ischeamic and angina, neuropathic pain disorders such as diabetic neuropathy, HIV neuropathy, chemotherapy induced neuropathies, post-herpetic neuralgia, post traumatic neuralgia and complex regional syndrome as well as itch.

Another embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of gastro-esophageal reflux disease, functional gastrointestinal disorders, irritable bowel syndrome, irritable bowel syndrome and functional dyspepsia.

A further embodiment of the invention relates to the use of the compounds of formula I as hereinbefore defined, for treatment of overactive bladder.

Yet a further embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, for the treatment of respiratory diseases selected from the group comprising of cough, asthma, chronic obstructive lung disease and emphysema, lung fibrosis and interstitial lung disease.

One embodiment of the invention relates to the use of the compound of formula I as hereinbefore defined, in the manufacture of a medicament for treatment of VR1 mediated

disorders and for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases, and any other disorder mentioned above.

Another embodiment of the invention relates to a method of treatment of VR1 mediated disorders and acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases, and any other disorder mentioned above, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compounds of formula I, as hereinbefore defined.

A further embodiment of the invention relates to a pharmaceutical composition comprising a compound of formula I as hereinbefore defined, for use in treatment of VR1 mediated disorders and for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases, and any other disorder mentioned above.

In the context of the present specification, the term "therapy" and "treatment" includes prevention and prophylaxis, unless there are specific indications to the contrary. The terms "treat","therapeutic" and "therapeutically" should be construed accordingly.

In this specification, unless stated otherwise, the term "inhibitor" and "antagonist" mean a compound that by any means, partly or completely, blocks the transduction pathway leading to the production of a response by the ligand.

The term "disorder", unless stated otherwise, means any condition and disease associated with vanilloid receptor activity.

Non- Medical use

In addition to their use in therapeutic medicine, the compounds of the invention, or salts, solvates or solvated salts thereof, are also useful as pharmacological tools in the

development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of VR1 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

Pharmaceutical composition

According to one embodiment of the present invention there is provided a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of the compound of formula I, or salts, solvates or solvated salts thereof, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration e.g. as an ointment, patch or cream or for rectal administration e.g. as a suppository.

In general the above compositions may be prepared in a conventional manner using one or more conventional excipients, pharmaceutical acceptable diluents and/or inert carriers.

Suitable daily doses of the compounds of formula I in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration.

The typical daily dose of the active ingredient varies within a wide range and will depend on various factors such as the relevant indication, severity of the illness being treated, the route of administration, the age, weight and sex of the patient and the particular compound being used, and may be determined by a physician.

Examples of pharmaceutical composition

The following illustrate representative pharmaceutical dosage forms containing a compound of formula I, or salts, solvates or solvated salts thereof, (hereafter compound X) for preventive or therapeutic use in mammals:

(a): Tablet	**mg/tablet**
Compound X	100
Lactose	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Capsule	**mg/capsule**
Compound X	10
Lactose	488.5
Magnesium stearate	1.5

(c): Injection	**(50 mg/ml)**
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	up to 100%

The above compositions may be obtained by conventional procedures well known in the pharmaceutical art.

Methods of Preparation

General methods of preparation

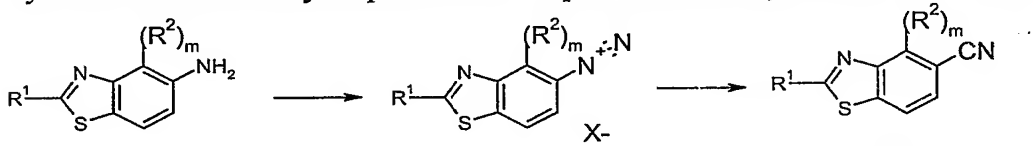
One embodiment of the invention relates to a process for the preparation of the compound of formula I, wherein R^1 to R^4, m, n and p, are as defined above, comprising;

IIa IV

a-i) cyanidation of compound of formula IIa through metal halogen exchange.

This reaction may be performed in any manner known to the skilled person in the art.

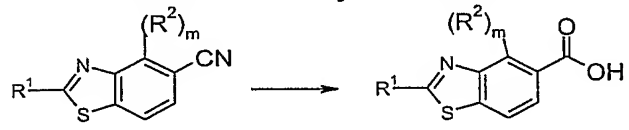
Cyanide formation may be performed via palladium catalyzed reaction with zinc cyanide.



IIc III IV

a-ii) Reaction of an aromatic amine of formula (IIc) with sodium nitrite in the presence of an acid like HCl, H_2SO_4 or TFA, to obtain a diazonium intermediate (III), that is reacted in-situ with sulphur dioxide or in the presence of copper chloride to give cyanide of formula IV.

This reaction may be performed in any manner known to the skilled person in the art. Suitable solvents to be used for this reaction may be water, acetone, organic acids such as acetic acid and TFA, or mixtures thereof. The temperature may be between 0 and 10 °C and the reaction time may be between 0.5 and 30 h.

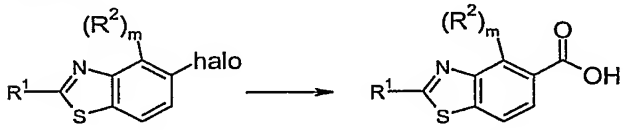


IV V

b) Hydrolysis of an aromatic cyanide of formula IV to obtain the carboxylic acid of formula V.

This reaction may be performed in any manner known to the skilled person in the art. Under acidic conditions, suitable solvents may be water, hydrochloridric acid, sulphuric

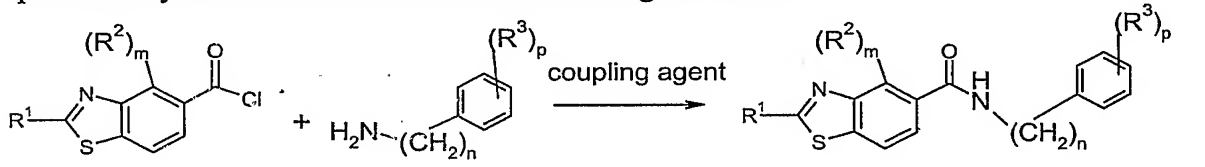
acid, or any mixtures thereof. Alternatively, it can be done in basic conditions by reaction with a suitable inorganic base in water or organic solvents like methanol, ethanol, iso-propanol or tert-butanol, or mixtures thereof. The temperature may be between 70 and 100°C.



IIa V

c) A metal halogen exchange followed by carbonylation with carbone dioxide to obtain the compound of formula V.

This reaction may be performed in any manner known to the skilled person in the art. Metal halogen exchange may be achieved with alkyl lithium or dialkyl magnesium Suitable solvents to be used for this reaction may be ethers such as ethyl ether, tetrahydrofuran and dioxin, or any mixtures thereof. The temperature may be between -60 and -70°C and the reaction time may be between 1 and 3 h. The lithium or magnesium spiecies may be reacted with carbon dioxide as gas or solid.



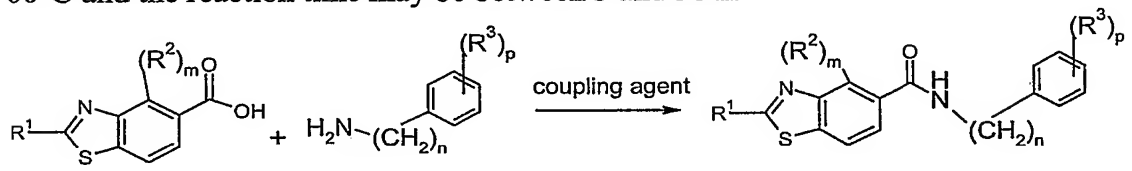
VI VII I

c)

d) reaction of the aromatic acyl chloride of formula VI with properly substituted amines of formula VII.

This reaction may be performed in any manner known to the skilled person in the art. Suitable solvents to be used for this reaction may be tertiary amides such as dimethylformamide and dimethylacetamide, halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxan or any mixtures thereof. Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine

and ethyl diisopropylamine may be used as well. The temperature may be between 10 and 60°C and the reaction time may be between 3 and 30 h.



V VII I

e) Reaction of the carboxylic acids of formula V with the aromatic amine of formula VII. Suitable solvents to be used for this reaction may be tertiary amides such as dimethylformamide and dimethylacetamide, halogenated hydrocarbons such as chloroform, dichloromethane and dichloroethane or aromatic and heteroaromatic compounds such as benzene, toluene, xylene, pyridine and lutidine or ethers such as ethyl ether, tetrahydrofuran and dioxin, or any mixtures thereof. Catalysts such as heteroaromatic bases like pyridine and lutidine or tertiary amines like triethylamine, *N*-methylmorpholine and ethyl diisopropylamine may be used as well. The temperature may be between 10 and 60°C and the reaction time may be between 3 and 30 h.

Intermediates

A further embodiment of the invention relates to compound 2-methyl-1,3-benzothiazole-5-carboxylic acid, which may be used as intermediate in the preparation of compounds suited for the treatment of VR1 mediated disorders, especially for use as intermediate for the preparation of compounds of formula I.

Examples

The invention will now be illustrated by the following Examples in which, generally :

(i) operations were carried out at ambient or room temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) was performed on Silicycle silica gel (grade 230-400 mesh, 60 Å, cat. Numb. R10030B) or obtained from Silicycle, Quebec, Canada or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Phenomenex, Luna C-18 100Å preparative reversed-phase column;

(iv) the ^{1}H NMR spectra were recorded on a Varian or Brucker at 400 or 600 MHz.

(v) the mass spectra were recorded utilising electrospray (LC-MS; LC:Waters 2790, column XTerra MS C_8 2.5 μm 2.1X30 mm, buffer gradient H_2O+0.1%TFA:CH_3CN+0.04%TFA, MS: micromass ZMD// ammonium acetate buffer) ionisation techniques;

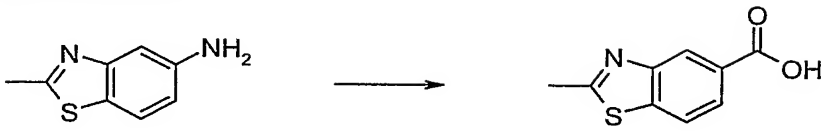
(vi) yields, where present, are not necessarily the maximum attainable;

(vii)intermediates were not necessarily fully purified but their structures and purity were assessed by thin layer chromatographic, HPLC and/or NMR analysis;

(viii) the following abbreviations have been used:

HPLC	high performance liquid chromatography
LC	liquid chromatography
MS	mass spectometry
ret. time	retention time
AcCl	acetyl chloride
DCM	dichloromethane
DMAP	dimethylaminopyridine
DMF	dimethylformamide
EtOH	ethanol
EtOAc	ethyl acetate
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium Hexafluorophosphate
HCl	hydrochloric acid
MeOH	methanol
THF	tetrahydrofurane

Intermediate 1



2-methyl-1,3-benzothiazole-5-carboxylic acid.

A solution of 2-methyl-5-aminobenzothiazole (10.0 g, 61.1 mmol) in acetone (250 mL) was cooled to 0 °C, and concentrated HCl (13.5 mL) was added. A solution of $NaNO_2$ (5.22 g, 75.7 mmol) in water (75.0 mL) was added in one portion to the first solution. The resulting mixture was stirred for 3 minutes, and a solution of KI (20.4 g, 123 mmol) in water (75.0 mL) was added. The mixture was stirred for an additional 10 minutes and then concentrated under reduced pressure to yield a residue, which was dissolved in a 9:1 mixture of DCM and MeOH and washed with a saturated solution of $NaHCO_3$. The organic fraction was washed with brine, dried with Na_2SO_4, filtered, concentrated under reduced pressure and dried under high vacuum. The resulting iodide, $ZnCN_2$ (7.17 g, 61.1 mmol) and $Pd(PPh_3)_4$ (2.00 g, 1.73 mmol) were mixed in DMF (200 mL) and heated to 100 °C for 12 hours, under a N_2 atmosphere. The solution was then cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with a saturated solution of $NaHCO_3$ followed by brine. The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure to yield the nitrile. ^{1}H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.89 (s, 3 H) 7.58 (dd, *J*=8.40, 1.56 Hz, 1 H) 7.93 (d, *J*=8.20 Hz, 1 H) 8.22 (d, *J*=0.98 Hz, 1 H); MS [M+] calcd. 174.0, found 174.8. A solution of the nitrile in 6.70 N HCl (150 mL) was refluxed for 12 hours. The solution was cooled to room temperature and then concentrated under reduced pressure. The product was purified by flash chromatography on reverse phase silica gel eluting with mixtures of EtOH and water (15/85 to 90/10) (4.45 g, 19.5 mmol, 32% for 3 steps). ^{1}H NMR (600 MHz, DMSO-D6) δ ppm 2.81 (s, 3 H) 7.92 (d, *J*=8.45 Hz, 1 H) 8.14 (d, *J*=8.45 Hz, 1 H) 8.38 (s, 1 H); MS [M+] cacld. 193.0, found 193.8.

Examples 1

***N*-4-*tert*-butylphenyl-2-methyl-1,3-benzothiazole-5-carboxamide.**

2-Methyl-1,3-benzothiazole-5-carboxylic acid (90.0 mg, 0.400 mml) was dissolved in DMF (3.00 mL), and HATU (190 mg, 0.500 mmol), 4-*tert*-butylaniline (75.0 mg, 0.500 mmol) and Et_3N (0.100 mL) were added. The mixture was stirred for 3 hours, and the solvents were evaporated. The product was purified by flash chromatography on silica gel eluting with mixtures of hexane and EtOAc (9:1 to 4:1) to yield the product (42.0 mg, 0.129 mmol, 32.0%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.27 (s, 9 H) 2.83 (s, 3 H) 4.90 - 5.18 (br s, 1 H) 7.36 (d, *J*=8.98 Hz, 2 H) 7.71 (dd, *J*=8.98, 2.73 Hz, 2 H) 7.96 (dd, *J*=8.40, 1.76 Hz, 1 H) 8.16 (d, J=8.40 Hz, 1H) 8.51 (d, *J*=1.37 Hz, 1 H) 10.31 (s, 1 H); MS [M+H] calcd. 325.0, found 325.0.

Examples 2

***N*-4-cyclohexylphenyl-2-methyl-1,3-benzothiazole-5-carboxamide.**

2-Methyl-1,3-benzothiazole-5-carboxylic acid (100 mg, 0.440 mml) was dissolved in DMF (5.00 mL), and HATU (190 mg, 0.500 mmol), 4-cyclohexylaniline (88.0 mg, 0.500 mmol) and Et_3N (0.100 mL) were added. The mixture was stirred for 3 hours, and the solvents were evaporated. The product was purified by flash chromatography on silica gel eluting with mixtures of hexane and EtOAc (9:1 to 4:1) to yield a mostly pure product, which was recrystallized from heptanes and EtOAc to yield a pure product (15.1 mg, 0.043 mmol, 10.0%). ^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.15 - 1.50 (m, 5 H) 1.60 - 1.83 (m, 6 H) 2.82 (s, 3 H) 7.18 (d, *J*=8.59 Hz, 2 H) 7.67 (d, *J*=8.59, 2 H) 7.94 (dd, *J*=8.40, 1.76 Hz, 1 H) 8.14 (d, *J*=8.40 Hz, 1 H) 8.48 (d, *J*=1.56 Hz, 1 H) 10.30 (s, 1 H); MS [M+] calcd. 350.2, found 351.0.

Examples 3

2-methyl-*N*-[2-methyl-4-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide.

2-Methyl-1,3-benzothiazole-5-carboxylic acid (90.0 mg, 0.470 mmol) was mixed with 2-methyl-4-trifluoromethylaniline (123 mg, 0.700 mmol), EDC (134 mg, 0.700 mmol) and DMAP (85.0 mg, 0.700 mmol) in DCM (5.00 mL) and DMF (3.00 mL) for 48 hours. The

mixture was concentrated, and the product was purified by flash chromatography on silica gel, eluting with mixtures of heptanes and EtOAc (95/5 to 75/25), to yield the product (14.0 mg, 0.0400 mmol, 8.50%). ^{1}H NMR (600 MHz, CHLOROFORM-D) δ ppm 2.42 (s, 3 H) 2.89 (s, 3 H) 7.50 (s, 1 H) 7.54 (d, J=8.45 Hz, 1 H) 7.85 - 8.05 (m, 3 H) 8.32 (d, J=8.45 Hz, 1 H) 8.41 (s, 1 H); MS [M+H] calcd. 351.0, found 351.0.

Examples 4

2-methyl-*N*-[4-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide.

2-Methyl-1,3-benzothiazole-5-carboxylic acid (150 mg, 0.660 mmol) was mixed with 4-trifluoromethylaniline (209 mg, 1.30 mmol), EDC (249 mg, 1.30 mmol) and DMAP (158 mg, 1.30 mmol) in DCM (5.00 mL) and DMF (2.00 mL) for 18 hours. The mixture was concentrated, and the product was purified by flash chromatography on silica gel, eluting with mixtures of heptanes and EtOAc (95/5 to 0/100), to yield the product (111 mg, 0.329 mmol, 50.0%). ^{1}H NMR (600 MHz, CHLOROFORM-D) δ ppm 2.85 (s, 3 H) 7.55 (d, J=8.45 Hz, 2 H) 7.84 (d, J=8.45 Hz, 2 H) 7.94 (dd, J=8.45, 1.79 Hz, 1 H) 8.04 (d, J=8.45 Hz, 1 H) 8.38 (d, J=1.02 Hz, 1 H); MS [M+H] calcd. 337.0, found 337.0.

Examples 5

2-methyl-*N*-[3-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide.

2-Methyl-1,3-benzothiazole-5-carboxylic acid (150 mg, 0.660 mmol) was mixed with 3-trifluoromethylaniline (209 mg, 1.30 mmol), EDC (249 mg, 1.30 mmol) and DMAP (158 mg, 1.30 mmol) in DCM (5.00 mL) and DMF (2.00 mL) for 18 hours. The mixture was concentrated, and the product was purified by flash chromatography on silica gel, eluting with mixtures of heptanes and EtOAc (95/5 to 50/25), to yield the product (58.1 mg, 0.173 mmol, 26.2%). ^{1}H NMR (600 MHz, CHLOROFORM-D) δ ppm 2.83 (s, 3 H) 7.33 (d, *J*=7.94 Hz, 1 H) 7.45 (t, *J*=7.94 Hz, 1 H) 7.85 (d, *J*=7.94 Hz, 1 H) 7.90 - 7.96 (m, 1 H) 8.03 (t, *J*=8.19 Hz, 1 H) 8.08 (s, 1 H) 8.39 (s, 1 H); MS [M+H] calcd. 337.0, found 337.0.

Examples 6

2-methyl-*N*-[2-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide.

2-Methyl-1,3-benzothiazole-5-carboxylic acid (150 mg, 0.660 mmol) was mixed with 2-trifluoromethylbenzylamine (228 mg, 1.30 mmol), EDC (249 mg, 1.30 mmol) and DMAP (158 mg, 1.30 mmol) in DCM (5.00 mL) and DMF (2.00 mL) for 18 hours. The mixture was concentrated, and the product was purified by flash chromatography on silica gel, eluting with mixtures of heptanes and EtOAc (95/5 to 50/25), to yield the product (123 mg, 0.350 mmol, 53.3%). ^{1}H NMR (600 MHz, MeOD) δ ppm 2.85 (s, 3 H) 4.70 (s, 2 H) 7.29 - 7.35 (m, 1 H) 7.43 - 7.50 (m, 2 H) 7.59 (d, J=7.68 Hz, 1 H) 7.87 - 7.92 (m, J=8.71 Hz, 1 H) 8.03 (d, J=8.45 Hz, 1 H) 8.31 (s, 1 H); MS [M+H] calcd. 351.0, found 351.0.

Examples 7

2-methyl-*N*-[4-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide.

2-Methyl-1,3-benzothiazole-5-carboxylic acid (150 mg, 0.660 mmol) was mixed with 4-trifluoromethylbenzylamine (228 mg, 1.30 mmol), EDC (249 mg, 1.30 mmol) and DMAP (158 mg, 1.30 mmol) in DCM (5.00 mL) and DMF (2.00 mL) for 18 hours. The mixture was concentrated, and the product was purified by flash chromatography on silica gel, eluting with mixtures of heptanes and EtOAc (95/5 to 50/25), to yield the product (114 mg, 0.325 mmol, 49.2%). ^{1}H NMR (600 MHz, MeOD) δ ppm 2.84 (s, 3 H) 4.56 (s, 2 H) 7.43 (d, J=7.94 Hz, 2 H) 7.51 (d, J=8.19 Hz, 2 H) 7.88 (d, J=8.45 Hz, 1 H) 8.02 (dd, J=8.45, 2.30 Hz, 1 H) 8.27 - 8.33 (m, J=1.02 Hz, 1 H); MS [M+H] calcd. 351.0, found 351.0.

Examples 8

2-methyl-*N*-[3-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide.

2-Methyl-1,3-benzothiazole-5-carboxylic acid (150 mg, 0.660 mmol) was mixed with 3-trifluoromethylbenzylamine (228 mg, 1.30 mmol), EDC (249 mg, 1.30 mmol) and DMAP (158 mg, 1.30 mmol) in DCM (5.00 mL) and DMF (2.00 mL) for 18 hours. The mixture was concentrated, and the product was purified by flash chromatography on silica gel, eluting with mixtures of heptanes and EtOAc (95/5 to 50/50), to yield the product (131 mg, 0.370 mmol, 57.0%). ^{1}H NMR (600 MHz, MeOD) δ ppm 2.84 (s, 3 H) 4.56 (s, 2 H) 7.43

(s, 2 H) 7.53 (d, J=7.42 Hz, 1 H) 7.56 (s, 1 H) 7.87 (dd, J=8.45, 1.54 Hz, 1 H) 8.01 (d, J=8.45 Hz, 1 H) 8.29 (s, 1 H); MS [M+H] calcd. 351.0, found 351.0.

Examples 9

***N*-4-methoxy-2-naphthyl-2-methyl-1,3-benzothiazole-5-carboxamide.**

2-Methyl-1,3-benzothiazole-5-carboxylic acid (200 mg, 1.03 mmol) was mixed with 4-methoxynaphthalen-2-amine (358 mg, 1.03 mmol), EDC (240 mg, 1.25 mmol) and DMAP (153 mg, 1.25 mmol) in DCM (10.0 mL) for 18 hours. The mixture was concentrated, and the product was purified by flash chromatography on silica gel, eluting with mixtures of heptanes and EtOAc (95/5 to 75/25), to yield the product (95.0 mg, 0.270 mmol, 27.0%). ^{1}H NMR (600 MHz, DMSO-D6) δ ppm 2.87 (s, 3 H) 3.99 (s, 3 H) 7.38 - 7.43 (m, 1 H) 7.46 (d, J=2.05 Hz, 1 H) 7.48 - 7.53 (m, 1 H) 7.82 (d, J=8.19 Hz, 1 H) 8.01 - 8.10 (m, 2 H) 8.16 (d, J=4.86 Hz, 1 H) 8.22 (d, J=8.45 Hz, 1 H) 8.62 (d, J=1.28 Hz, 1 H) 10.53 (s, 1 H); MS [M+H] calcd. 349.0, found 349.0.

Examples 10-21

The following examples were prepared by the general procedure of Example 1- 9 using 2-Methyl-1,3-benzothiazole-5-carboxylic acid (Intermediate 1) and the appropriate amine as indicated in the below table.

Ex.	Chemical name	Mass calcd.	Mass found	Proton NMR	Amine
10	N-(4-bromophenyl)-2-methyl-1,3-benzothiazole-5-carboxamide	347.0	346.7	(600 MHz, DMSO-D6) δ ppm 2.84 (s, 3 H) 7.55 (d, J=8.70 Hz, 2 H) 7.80 (d, J=8.70 Hz, 2 H) 7.96 (d, J=8.19 Hz, 1 H) 8.19 (d, J=8.45 Hz, 1 H) 8.52 (s, 1 H) 10.49 (s, 1 H)	(4-bromophenyl)amine

Ex.	Chemical name	Mass calcd.	Mass found	Proton NMR	Amine
11	2-methyl-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-carboxamide	311.1	311.0	(600 MHz, DMSO-D6) δ ppm 2.26 (s, 3 H) 2.80 - 2.85 (m, 5 H) 3.49 (q, J=6.66 Hz, 2 H) 7.09 - 7.15 (m, 4 H) 7.85 (d, J=8.45 Hz, 1 H) 8.11 (d, J=8.19 Hz, 1 H) 8.35 (s, 1 H) 8.71 (s, 1 H)	[2-(4-methylphenyl)ethyl]-amine
12	N-[2-(3-fluorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide	315.1	315.0	(600 MHz, DMSO-D6) δ ppm 2.83 (s, 3 H) 2.90 (t, J=7.17 Hz, 2 H) 3.54 (q, J=6.91 Hz, 2 H) 7.01 - 7.06 (m, 1 H) 7.10 (t, J=6.91 Hz, 2 H) 7.31 - 7.36 (m, 1 H) 7.84 (dd, J=8.45, 1.28 Hz, 1 H) 8.11 (d, J=8.45 Hz, 1 H) 8.34 (s, 1 H) 8.72 (t, J=5.12 Hz, 1 H)	[2-(3-fluorophenyl)ethyl]-amine
13	N-(5-isopropoxy-1-naphthyl)-2-methyl-1,3-benzothiazole-5-carboxamide	377.1	377.0	(400 MHz, DMSO-D6) δ ppm 1.29 (d, J=6.05 Hz, 6 H) 2.86 (s, 3 H) 4.62 - 4.73 (m, 1 H) 7.21 (dd, J=8.89, 2.44 Hz, 1 H) 7.28 (d, J=2.15 Hz, 1 H) 7.38 (t, J=7.71 Hz, 1 H) 7.55 (d, J=7.23 Hz, 1 H) 7.78 (d, J=8.01 Hz, 1 H) 7.90 (d, J=8.98 Hz, 1 H) 8.06 (dd, J=8.30, 1.46 Hz, 1 H) 8.22 (d, J=8.40 Hz, 1 H) 8.63 (s, 1 H) 10.46 (s, 1 H)	5-isopropoxynaphthalen-1-amine

Ex.	Chemical name	Mass calcd.	Mass found	Proton NMR	Amine
14	2-methyl-N-{2-[4-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazole-5-carboxamide	365.1	365.0	(400 MHz, CD3OD) δ ppm 2.85 (s, 3 H) 3.03 (t, J=7.23 Hz, 2 H) 3.67 (t, J=7.23 Hz, 2 H) 7.47 (d, J=8.01 Hz, 2 H) 7.60 (d, J=8.01 Hz, 2 H) 7.79 (dd, J=8.40, 1.76 Hz, 1 H) 8.00 (d, J=8.40 Hz, 1 H) 8.28 (d, J=1.76 Hz, 1 H).	{2-[4-(trifluoromethyl)-phenyl]ethyl}amine
15	N-[2-(4-ethylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide	325.1	325.0	(400 MHz, CD3OD) δ ppm 1.19 (t, J=7.62 Hz, 3 H) 2.59 (q, J=7.62 Hz, 2 H) 2.84 (s, 3 H) 2.90 (t, J=7.42 Hz, 2 H) 3.60 (t, J=7.42 Hz, 2 H) 7.12 (d, J=8.20 Hz, 2 H) 7.17 (d, J=8.20 Hz, 2 H) 7.79 (dd, J=8.40, 1.56 Hz, 1 H) 7.99 (d, J=8.40 Hz, 1 H) 8.28 (d, J=1.37 Hz, 1 H).	[2-(4-ethylphenyl)ethyl]-amine
16	N-[2-(4-fluorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide	315.1	315.0	(400 MHz, CD3OD) δ ppm 2.85 (s, 3 H) 2.93 (t, J=7.32 Hz, 2 H) 3.61 (t, J=7.32 Hz, 2 H) 7.01 (ddd, J=8.89, 6.64, 2.05 Hz, 1 H) 7.23 - 7.32 (m, 2 H) 7.79 (dd, J=8.40, 1.76 Hz, 2 H) 7.99 (d, J=8.40 Hz, 1 H) 8.27 (d, J=1.76 Hz, 1 H).	[2-(4-fluorophenyl)ethyl]-amine

Ex.	Chemical name	Mass calcd.	Mass found	Proton NMR	Amine
17	N-[2-(4-tert-butylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide	353.1	353.0	(400 MHz, CD3OD) δ ppm 1.29 (s, 9 H) 2.85 (s, 3 H) 2.90 (t, J=7.42 Hz, 2 H) 3.60 (t, J=7.42 Hz, 2 H) 7.19 (d, J=8.20 Hz, 2 H) 7.33 (d, J=8.40 Hz, 2 H) 7.80 (d, J=8.40 Hz, 1 H) 7.99 (d, J=8.40 Hz, 1 H) 8.29 (s, 1 H).	[2-(4-*tert*-butylphenyl)-ethyl]amine
18	N-[2-(4-methoxyphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide	327.1	327.0	(400 MHz, CD3OD) δ ppm2.84 (s, 3 H) 2.87 (t, J=7.44 Hz, 2 H) 3.58 (t, J=7.32 Hz, 2 H) 3.74 (s, 3 H) 6.84 (d, J=8.79 Hz, 2 H) 7.17 (d, J=8.59 Hz, 2 H) 7.79 (dd, J=8.40, 1.76 Hz, 1 H) 7.98 (d, J=8.40 Hz, 1 H) 8.27 (d, J=1.37 Hz, 1 H).	[2-(4-methoxyphenyl)-ethyl]amine
19	N-(4-isopropylphenyl)-2-methyl-1,3-benzothiazole-5-carboxamide	311.1	311.0	(400MHz, CD3OD) δ ppm 1.24 (d, J = 7.0 Hz, 6H) 2.83-2.93 (m, 1H) 2.97 (s, 3H) 7.19-7.26 (m, 2H) 7.55-7.63 (m, 2H) 8.04 (dd, J = 1.7, 8.5 Hz, 1H) 8.15 (d, J = 8.6 Hz, 1H) 8.46 (d, J = 1.4 Hz, 1H)	4-isopropylaniline

Ex.	Chemical name	Mass calcd.	Mass found	Proton NMR	Amine
20	N-[2-(4-chlorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide	331.0	330.8	(400MHz, CD3OD) δ ppm 2.86-2.95 (m, 5H) 3.61 (t, J = 7.3 Hz, 2H) 7.17-7.30 (m, 4H) 7.84 (dd, J = 1.7, 8.5 Hz, 1H) 8.06 (d, J = 8.6 Hz, 1H) 8.28 (d, J = 1.8 Hz, 1H)	[2-(4-chlorophenyl)-ethyl]amine
21	N-[2-(3,4-dichlorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide	365.0	364.8	(400MHz, CD3OD) δ ppm 2.86-2.96 (m, 5H) 3.61 (t, J = 7.1 Hz, 2H) 7.18 (dd, J = 2.2, 8.2 Hz, 1H) 7.37-7.45 (m, 2H) 7.84 (dd, J = 1.8, 8.4 Hz, 1H) 8.06 (d, J = 8.6 Hz, 1H) 8.27 (d, J = 1.6 Hz, 1H)	[2-(3,4-dichlorophenyl)-ethyl]amine

Examples 22

***N*-4-*tert*-butylphenyl-2-hydroxymethyl-1,3-benzothiazole-5-carboxamide.**

2-Methyl-1,3-benzothiazole-5-carboxylic acid (430 mg, 1.89 mmol) and SeO_2 (628 mg, 5.65 mmol) were mixed in dioxane (50.0 mL) and heated to 100 °C for 18 hours. The mixture was evaporated to dryness and then dissolved in MeOH (10.0 mL). $NaBH_4$ (214 mg, 5.65 mmol) was added, and the mixture was stirred for 20 minutes. The mixture was evaporated to dryness, and the residue was dissolved in DCM (25.0 mL). AcCl (599 mg, 7.60 mL) was added, followed by Et_3N (769 mg, 7.60 mmol). The mixture was stirred for 30 minutes and then evaporated to dryness. The residue was dissolved in DCM (25.0 mL) and aniline (1.06 g, 11.3 mmol) and Et_3N (218 mg, 2.15 mmol) were added. The mixture was stirred for 30 minutes and then washed with a saturated solution of $NaHCO_3$ followed by 1N HCl. The organic phase was dried with Na_2SO_4, filtered and concentrated to yield a mostly pure compound (399 mg, 1.59 mmol, 84.0%). The resulting product, 2-

hydroxymethyl-1,3-benzothiazole-5-carboxylic acid, (150 mg, 0.600 mmol) was mixed with the 4-*tert*-butylaniline (173 mg, 0.900 mmol), EDC (110 mg, 0.900 mmol) and DMAP (134 mg, 0.900 mmol) in DCM (5.00 mL) for 12 hours. The mixture was washed with a saturated solution of $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated. The residue was dissolved in THF (3.00 mL), and a 1N solution of NaOH (3.00 mL) was added. The mixture was stirred for 1 hour, and then evaporated to dryness. The product was purified by flash chromatography on silica gel, eluting with mixtures of heptanes and EtOAc (80/20 to 50/50) to yield the product (43.1 mg, 0.130 mmol, 22.0% 2 steps). ^{1}H NMR (600 MHz, MeOD) δ ppm 1.22 (s, 9 H) 4.90 (s, 2 H) 7.30 (d, J=8.70 Hz, 2 H) 7.50 (d, J=8.70 Hz, 2 H) 7.89 (d, J=8.45 Hz, 1 H) 8.04 (dd, 1 H) 8.37 (d, J=1.28 Hz, 1 H); MS calcd. [M+H] 341.0, found 341.0.

Examples 23

2-(hydroxymethyl)-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-carboxamide.

2-Methyl-*N*-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-carboxamide, example 11, (280 mg, 0.9 mmol) was dissolved in 10 mL of dioxane. Grounded selenium dioxide (485 mg, 4.37 mmol, 4.85 equiv) was added and the mixture heated in a sealed tube at 100°C overnight. After cooling to room temperature, the mixture was filtered over Celite (rinced with methanol) and the filtrated evaporated to dryness. The residue was dissolved in 15 mL of methanol, sodium borohydride (105 mg, 2.78 mmol, 3.1 equiv) was added in small portions and the mixture stirred for 20 min. Volatiles were evaporated, the residue was dissolved in ethyl acetate, washed with water, dried over magnesium sulfate, filtered and evaporated to dryness. The crude product was purified by reverse-phase HPLC (water acetonitrile 80:20 to 5:95) to yield the product (105 mg, 0.24 mmol, 27%) as the TFA salt. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.29 (s, 3 H) 2.89 (t, J=7.42 Hz, 2 H) 3.60 (t, J=7.42 Hz, 2 H) 4.97 (s, 2 H) 7.10 (d, J=7.80 Hz, 2 H) 7.15 (d, J=7.60 Hz, 2 H) 7.81 (dd, J=8.40, 1.56 Hz, 1 H) 8.06 (dd, J=8.40, 0.59 Hz, 1 H) 8.30 (dd, J=1.76, 0.39 Hz, 1 H); MS [M+H] calcd. 327.1, found 327.0.

Examples 24

N-[2-(3-fluorophenyl)ethyl]-2-(hydroxymethyl)-1,3-benzothiazole-5-carboxamide.

The crude N-[2-(3-fluorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide, example 12, (~1 mmol) was dissolved in 10 mL of dioxane. Grounded selenium dioxide (485 mg, 4.37 mmol, 4.85 equiv) was added and the mixture heated in a sealed tube at 95°C overnight. After cooling to room temperature, volatiles were evaporated and the residue was dissolved in 10 mL of methanol. Sodium borohydride (105 mg, 2.78 mmol, 3.1 equiv) was added in small portions and the mixture stirred for 20 min. Volatiles were evaporated, the residue was dissolved in ethyl acetate, washed with water, dried over magnesium sulfate, filtered and evaporated to dryness. The crude product was purified by reverse-phase HPLC (water acetonitrile 70:30 to 50:50) yielding the product (87 mg , 0.2 mmol, 20% global yield, including preparation of example 12) as the TFA salt. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.29 (s, 3 H) 2.89 (t, J=7.42 Hz, 2 H) 3.60 (t, J=7.42 Hz, 2 H) 4.97 (s, 2 H) 7.10 (d, J=7.80 Hz, 2 H) 7.15 (d, J=7.60 Hz, 2 H) 7.81 (dd, J=8.40, 1.56 Hz, 1 H) 8.06 (dd, J=8.40, 0.59 Hz, 1 H) 8.30 (dd, J=1.76, 0.39 Hz, 1 H);); MS [M+H] calcd. 331.1, found 331.0.

Pharmacology

1. hVR1 FLIPR (Fluorometric Image Plate Reader) screening assay

Transfected CHO cells, stably expessing hVR1 (15,000 cells/well) are seeded in 50 ul media in a black clear bottom 384 plate (Greiner) and grown in a humidified incubator (37°C, 2% CO_2), 24-30 hours prior to experiment.

Subsequently, the media is removed from the cell plate by inversion and 2 μM Fluo-4 is added using a multidrop (Labsystems). Following the 40 minutes dye incubation in the dark at 37°C and 2% CO_2, the extracellular dye present is washed away using an EMBLA (Scatron), leaving the cells in 40ul of assay buffer (1 X HBSS, 10 mM D-Glucose, 1 mM $CaCl_2$, 10 mM HEPES, 10 X 7.5% $NaHCO_3$ and 2.5 mM Probenecid).

FLIPR assay - IC_{50} determination protocol

For IC_{50} determinations the fluorescence is read using FLIPR filter 1 (em 520-545 nM). A cellular baseline recording is taken for 30 seconds, followed by a 20 µl addition of 10, titrated half-log concentrations of the test compound, yielding cellular concentration ranging from 3 µM to 0.1 nM. Data is collected every 2 seconds for a further 5 minutes prior to the addition of a VR1 agonist solution: either 50 nM solution of capsaicin or MES (2-[N-morpholino] ethanesulfonic acid) buffer (pH 5.2), by the FLIPR pipettor. The FLIPR continues to collect data for a further 4 minutes. Compounds having antagonistic properties against the hVR1 will inhibit the increase in intracellular calcium in response to the capsaicin addition. This consequently leading to a reduction in fluorescence signal and providing a reduced fluorescence reading, compared with no compound, buffer controls. Data is exported by the FLIPR program as a sum of fluorescence calculated under the curve upon the addition of capsaicin. Maximum inhibition, Hill slope and IC_{50} data for each compound are generated.

FLIPR (Fluorometric Image Plate Reader) screening assay with HEK T-REX hVR1.

HEK T-REX hVR1 inducible cells are grown in supplemented DMEM medium (10% FBS, 2 mM Glutamine, 5µg/ml Blasticidine & 350 µg/ml Zeocin). HEK cells are plated in 384-black polylysine coated plate (Costar) at 10000 cells/well/50µl for 24 hours or 5,500 cells /well 48 hours in a humidified incubator (5% CO_2 and 37°C) in DMEM medium without selection agent. HEK T-Rex hVR1 cells are induced with 0.1µg/ml Tetracycline 16 hours prior the experiment.

Subsequently, the media is removed from the cell plate by inversion and 2 µM Fluo-4 is added using a multidrop (Labsystems). Following the 30 to 40 minutes dye incubation in the dark at 37°C and 2% CO_2, the extracellular dye present is washed away using an MicroplateWasher Skatron Embla 384, leaving the cells in 25µl of assay buffer (1X HBSS without Ca^{++}/Mg^{++}/sodium bicarbonate, 1mM $CaCl_2$ & 5 mM D-Glucose).

FLIPR assay - IC_{50} determination protocol

For IC_{50} determinations the fluorescence is read using FLIPR filter 1 (em 520-545 nM). A cellular baseline recording is taken for 10 seconds, followed by 12,5 µl addition of test compounds, 10 points dilution 3 fold concentration, yielding cellular concentration ranging from 22.5 µM to 0.1 nM. Data are collected every 2 seconds for a further 5 minutes prior to the addition of a VR1 agonist solution: 20 nM (or 50 nM) capsaicin solution is added by the FLIPR pipettor. The FLIPR continues to collect data for a further 4 minutes. Compounds having antagonistic properties against the hVR1 will inhibit the increase in intracellular calcium in response to the capsaicin addition. This consequently leading to a reduction in fluorescence signal and providing a reduced fluorescence reading, compared with no compound, buffer controls. Data is exported by the FLIPR program as a sum of fluorescence calculated under the curve upon the addition of capsaicin. Maximum inhibition, Hill slope and IC_{50} data for each compound are generated.

List of abbreviations

VR1	vanilloid receptor 1
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
GERD	gastro-esophageal reflux disease
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
EGTA	Ethylene glycol-bis(2-aminoethylether)-*N,N,N′,N′*-tetraacetic acid
EMBLA	Skatron, Plate Cell Washer, from Molecular Devices company
FLIPR	Fluorometric Image Plate Reader
HBSS	Hank's Balanced Salt Solution
MES	(2-[N-Morphholino]ethanesulfonic acid) Hydrate, Sigma cat# M-5287
NUT	Nutrient mixture F-12, medium for culturing cells
MEM	Minimal Eagle Medium

Results

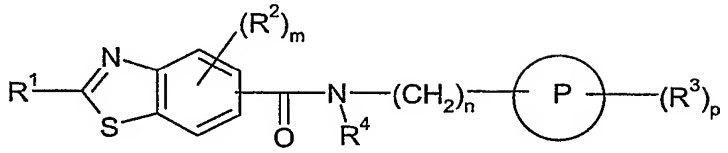
Typical IC_{50} values as measured in the assays described above are 10 μM or less. In one aspect of the invention the IC_{50} is below 500 nM.

Results from the hVR1 FLIPR

Example No.	**IC_{50} nM (agonist)**
1	226 (capsaicin)
7	2782(capsaicin)
8	1660 (capsaicin)

CLAIMS

1. A compound of formula I



(I)

wherein:

ring P is C_{6-10}aryl, C_{3-11}cycloalkyl or C_{5-10}heteroaryl;

R^1 is H, C_{1-4}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, $COOC_{0-6}$alkyl, NH_2, NHC_{1-6}alkyl, $N(C_{1-6}alkyl)_2$, NH(aryl) or $N(aryl)_2$;

R^2 is H, C_{1-4}alkyl, halo, hydroxyC_{0-6}alkyl or C_{1-6}alkylOC_{0-6}alkyl;

m is 0, 1, 2 or 3;

n is 0, 1, 2, 3, 4 or 5;

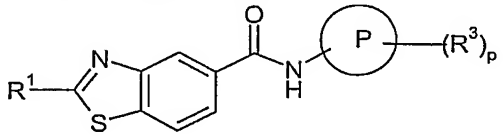
R^3 is NO_2, NH_2C_{0-6}alkyl, halo, $N(C_{1-6}alkyl)_2C_{0-6}$alkyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}haloalkyl, C_{1-6}haloalkylO, C_{5-6}arylC_{0-6}alkyl, C_{5-6}heteroarylC_{0-6}alkyl, C_{3-7}cycloalkylC_{0-6}alkyl, C_{3-7}heterocycloalkylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl, C_{1-6}alkylSC_{0-6}alkyl, C_{1-6}alkylNC_{0-6}alkyl, $(C_{0-6}alkyl)_2NC(O)C_{0-6}$alkyl, $(C_{0-6}alkyl)_2OC(O)C_{0-6}$alkyl or $(C_{0-6}alkyl)_2C(O)OC_{0-6}$alkyl;

p is 1, 2, 3, 4 or 5; and

R^4 is H, C_{1-6}alkyl, arylC_{0-6}alkyl, C_{1-6}alkylOC_{0-6}alkyl or $N(C_{1-6}alkyl)_2C_{0-6}$alkyl;

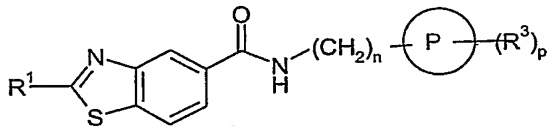
or salts, solvates or solvated salts thereof.

2. A compound of formula Ib wherein R^1, R^3, m and p, are as defined as in claim 1, and n is 0 and R^2 and R^4 are H.



(Ib)

3. A compound of formula Ic, wherein R^1, R^3, m and p, are as defined as in claim 1, and n is 1, 2, 3, 4 or 5 and R^2 and R^4 are H.



(Ic)

4. The compound according to any one of claims 1 or 3 wherein ring P is phenyl.

5. The compound according to any one of claims 1 or 3 wherein ring R^1 is is methyl or hydroxyC_{1-3}alkyl.

6. The compound according to any one of claims 1 to 3 wherein R^3 is tert-butyl, phenyl, fluoromethyl, difluoromethyl or trifluoromethyl.

7. The compounds selected from the group consisting of

N-4-*tert*-butylphenyl-2-methyl-1,3-benzothiazole-5-carboxamide,

N-4-cyclohexylphenyl-2-methyl-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[2-methyl-4-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[4-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[3-trifluoromethylphenyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[2-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[4-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide,

2-methyl-*N*-[3-trifluoromethylbenzyl]-1,3-benzothiazole-5-carboxamide,

N-4-methoxy-2-naphthyl-2-methyl-1,3-benzothiazole-5-carboxamide,

N-4-*tert*-butylphenyl-2-hydroxymethyl-1,3-benzothiazole-5-carboxamide,

N-(4-bromophenyl)-2-methyl-1,3-benzothiazole-5-carboxamide,

2-methyl-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-carboxamide,

N-[2-(3-fluorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,

N-(5-isopropoxy-1-naphthyl)-2-methyl-1,3-benzothiazole-5-carboxamide,

2-methyl-N-{2-[4-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazole-5-carboxamide,
N-[2-(4-ethylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,
N-[2-(4-fluorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,
N-[2-(4-tert-butylphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,
N-[2-(4-methoxyphenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,
N-(4-isopropylphenyl)-2-methyl-1,3-benzothiazole-5-carboxamide,
N-[2-(4-chlorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,
N-[2-(3,4-dichlorophenyl)ethyl]-2-methyl-1,3-benzothiazole-5-carboxamide,
N-4-tert-butylphenyl-2-hydroxymethyl-1,3-benzothiazole-5-carboxamide,
2-(hydroxymethyl)-N-[2-(4-methylphenyl)ethyl]-1,3-benzothiazole-5-carboxamide, and
N-[2-(3-fluorophenyl)ethyl]-2-(hydroxymethyl)-1,3-benzothiazole-5-carboxamide
or salts, solvates or solvated salts thereof.

8. The compound according to any one of claims 1 to 7, for use in therapy.

9. Use of the compound according to any one of claims 1 to 7, in treatment of VR1 mediated disorders.

10. The use according to claim 9 for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain.

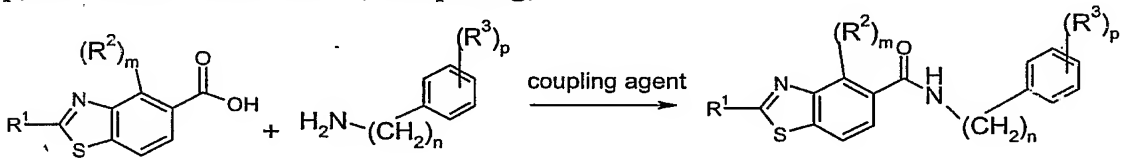
11. The use according to claim 9 for treatment of respiratory diseases.

12. A method of treatment of VR1 mediated disorders and for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases, comprising administrering to a mammal, including man in need of such treatment, a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 7.

13. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of formula I, according to any one of claims 1 to 7, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

14. The pharmaceutical formulation according to claim 13, for use in the treatment of VR1 mediated disorders and for treatment of acute and chronic pain, acute and chronic neuropathic pain and acute and chronic inflammatory pain, and respiratory diseases.

15. A process for the preparation of the compound of formula I, wherein R^1 to R^4, m, n and p, are defined as in claim 1, comprising;



V VII I

reaction of the carboxylic acids of formula V with aromatic amine of formula VII.

16. Use the compound 2-methyl-1,3-benzothiazole-5-carboxylic acid as intermediate in the preparation of the compound of formula I.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001964

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FILE REGISTRY, STN International RN 799259-85-1, 799259-84-0, 799259-83-9, 790716-55-1, 769961-89-9, 757944-90-4, 722461-64-5, 722461-59-8, 708281-65-6, 700856-69-5, 700849-95-2, 518992-70-6, 450353-93-2, 441746-32-3, 401823-58-3, 401823-56-1, 401823-54-9, 401823-50-5, 393518-16-6, 393518-15-5, 384848-12-8, 351437-84-8, 351190-26-6, 333420-14-7, .../... --	1-2,4-6,8
X	RN 326010-56-4, 326010-54-2, 325830-73-7, 313524-22-0, 225521-94-8, 225521-89-1, 225521-86-8, 796097-24-0, 785711-05-9, 785704-06-5, 785704-04-3, 681169-46-0 --	1-2,4-6,8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2006	03 -04- 2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001964

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9924035 A1 (BRISTOL-MYERS SQUIBB COMPANY), 20 May 1999 (20.05.1999), page 84, line 21, page 93, ex 181; page 95, line 16	1-2,8
	--	
X	WO 0158897 A1 (DARWIN DISCOVERY LIMITED), 16 August 2001 (16.08.2001), claim 8, lines 6 and 14	1-2,8
	--	
X	WO 03037847 A1 (SMITHKLINE BEECHAM P.L.C.), 8 May 2003 (08.05.2003), example 72	1,4
	--	
X	WO 9841508 A1 (SMITHKLINE BEECHAM PLC), 24 Sept 1998 (24.09.1998), claim 3, line 27	1-2,8
	--	
X	EP 0643057 A1 (BRISTOL-MYERS SQUIBB COMPANY), 15 March 1995 (15.03.1995), page 118, line 30, claim 14	1-2,8
	--	
X	JAGABANDHU DAS et al, "Molecular Design, Synthesis, and Structure-Activity Relationships Leading to the Potent and Selective P56lck Inhibitor BMS-243117", Bioorganic & Medicinal Chemistry Letters, 2003, volume 13, pages 2145-2149	1-2,4
	--	
X	JAGABANDHU DAS et al: "Discovery of 2-Amino-heteroaryl-benzothiazole-6-anilides as Potent p56lck Inhibitors", Bioorganic & Medicinal Chemistry Letters, 2003, volume 13, pages 2587-2590	1-2,4,8
	--	
X	WO 2004096784 A1 (ASTRAZENECA AB), 11 November 2004 (11.11.2004)	1-16
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International patent classification (IPC)

C07D 277/62 (2006.01)
A61K 31/381 (2006.01)
A61P 25/00 (2006.01)
C07D 277/64 (2006.01)
C07D 277/68 (2006.01)
C07D 277/82 (2006.01)

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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ SE2005/001964

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-12
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 9-12 relates to a method of treatment of the human or animal body by therapy /Rule 39.1(iv). Nevertheless, a search has been carried out for this claim, based on the alleged effects of the compounds.

2. ☒ Claims Nos.: 1-4, 5
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many

.../...

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Box II.2

documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to:
Compounds of formula I, where R1 is other than H. Some compounds where R1 is hydrogen have however been found and cited in the report.

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